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Modulation of pair bonding in female prairie voles (*Microtus ochrogaster*) by corticosterone

(glucocorticoids/adrenalectomy/monogamy)

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ABSTRACT **Glucocorticoid levels in animals may respond to and influence the development of social attachments. This hypothesis was tested in prairie voles (*Microtus ochrogaster*), monogamous rodents that form long-term heterosexual pair bonds. In socially naive female prairie voles, cohabitation with an unfamiliar male resulted in a dramatic decline in serum corticosterone levels. When corticosterone levels were reduced via adrenalectomy, females developed partner preferences after 1 h of cohabitation, while sham-operated and untreated females required 3 h or more of nonsexual cohabitation to establish a partner preference. In adrenalectomized and intact females, exogenous injections of corticosterone, given prior to social exposure, prevented the development of preferences for the cohabitating male. Although corticosterone inhibited the development of partner preferences, it did not interfere with the expression of previously established social preferences. These results suggest that social stimuli can modulate adrenal activity and that adrenal activity, in turn, is capable of influencing the formation of adult social preferences in female prairie voles. The involvement of the adrenal axis in the formation of partner preferences and the subsequent development of pair bonds provides a mechanism through which environmental and social factors may influence social organization in this species.**

Monogamy in mammals is characterized by the formation of heterosexual pair bonds, based on selective social attachments. However, monogamy is rare among mammals (1) and is particularly uncommon in rodents (2). Research on prairie voles, *Microtus ochrogaster*, small arvicoline rodents, has established this species as a monogamous mammal. Field and laboratory studies have revealed that prairie voles exhibit the following characteristics of monogamy: formation of long-term pair bonds between males and females, characterized by preference for a familiar partner and in some cases selective aggression toward strangers (3, 4); biparental care (2, 5, 6); reduced sexual dimorphism (2, 7); and reproductive suppression and incest avoidance in offspring that remain with the natal family (8, 9).

Patterns of reproductive physiology in monogamous mammals tend to be strongly influenced by social factors. Female prairie voles do not exhibit estrous cycles and naive females remain reproductively quiescent until behavioral estrus is induced by contact with an unfamiliar male (10, 11). Ovarian activation in female prairie voles occurs most reliably in the absence of family members (11) or stimuli from other females (12). Thus, a short latency to pair bonding may increase the probability of reproductive activation and dispersal from the natal nest. Research on the proximate regulation of pair-bond formation has focused on the effects of mating (13) and mating-related neuroendocrine changes (14, 15). To our knowledge, the mechanisms underlying pair bond formation during the period of nonsexual cohabitation that precedes behavioral estrus (13) have not been examined.

In the laboratory, the partner preference component of pair bonding has been measured by using tests in which an experimental animal can elect to spend time with a familiar animal (partner), an unfamiliar animal (stranger), or to remain alone. Tested in this manner, reliable partner preferences are exhibited after both sexual and nonsexual cohabitation (13). This measurement of partner preference becomes stable within 30–60 min and in females remains consistent, even after separation for ≈8 days (A.C.D., unpublished data).

Among the endocrine correlates of initial social interactions in mammals are fluctuations in the production of hormones of the hypothalamic–pituitary–adrenal axis, including glucocorticoids, such as corticosterone or cortisol. For example, in various mammalian species, adrenal glucocorticoid production increases during social separation (16, 17). Elevated adrenal glucocorticoid levels are routinely associated with disruptions in social attachments and may even be treated as an index of "social stress" (17). In the context of the development or maintenance of social attachments, the behavioral consequences of exposure to high levels of adrenal steroids remain unspecified.

The present study examines the hypothesis that corticosterone may participate in the development or expression of partner preference after a nonsexual interaction. These studies were stimulated by preliminary data indicating that basal levels of corticosterone were ≈10 times those typically measured in rats (ref. 18 and S.T. and C.S.C., unpublished data). In addition, the corticosterone response of prairie voles to unfamiliar social stimuli appeared to differ sharply from those reported in other rodents. In female mice, exposure to chemosignals from unfamiliar conspecifics was followed by a rapid increase in corticosterone (19). In contrast, when socially naive female prairie voles were introduced to an unfamiliar male, corticosterone levels declined significantly (18). The presence of high basal levels of corticosterone, coupled with an unusual endocrine response to opposite-sex conspecifics, suggested the possibility that corticosterone might have adaptive behavioral functions in prairie voles. The goals of the study described below were (*i*) to characterize the change in blood corticosterone levels over time in female prairie voles exposed to unfamiliar males and females, (*ii*) to assess the effects of endogenous and exogenous corticosterone on the development of partner preferences, and (*iii*) to assess the effects of corticosterone on the expression of partner preferences.

MATERIALS AND METHODS

Adult prairie voles (*M. ochrogaster*) used in this study were the F_3 generation of animals originally trapped near Urbana, Illinois. Animals were born and maintained in long days (14 h

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light/10 h dark; lights on at 0700 h), weaned at 21 days of age, and housed in same-sex sibling groups until random assignment to an experimental group at 60 days of age or older. Each experimental animal was housed individually for 2 weeks prior to random assignment to one of the experiments described below. Both the experimental and stimulus voles have intact gonads unless otherwise noted. All cohabitations were videotaped and screened for mating. The data from four animals that copulated during part of this study were not included in the analyses.

Blood samples were collected from the periorbital sinus under rapid gaseous anesthesia (Metofane; Pitman–Moore, Mundelein, IL). The entire blood sampling procedure lasted less than 1.5 min. Samples were assayed by using a ^{125}I-labeled corticosterone kit (ICN) that had been validated previously for use in prairie voles (S.T. and C.S.C., unpublished data). Because of the high basal levels of corticosterone in prairie voles, the serum was diluted 1:2121 in assay buffer. Samples were run in duplicate. The cross-reactivity with other steroids was <0.5%.

Experiment 1. The purpose of experiment 1 was to examine the reliability and specificity of our earlier observation in female prairie voles that corticosterone levels decline after exposure to an unfamiliar male. If a reduction in corticosterone levels is functionally related to the establishment of a heterosexual pair bond, then reductions in corticosterone levels in females would be expected upon exposure to an unfamiliar male but not after exposure to another female. In addition, we predicted that socially naive females, but not females with an established partner (paired females), would show declines in corticosterone. Therefore, serum corticosterone levels were measured in socially naive (unpaired) females after exposure to an unfamiliar male or an unfamiliar female. In a third group, paired females were separated from their established partner (a castrated male) after 3 days of cohabitation and immediately exposed to an unfamiliar male. The time course of corticosterone responses to these stimuli was established by using independent groups (Table 1) sampled prior to social exposure or after 15, 30, 60, or 180 min of exposure to the stimulus animal.

To compare changes in corticosterone levels across time after exposure to an unfamiliar animal (Table 1), data within each experimental group were analyzed by ANOVA. After a significant ANOVA ($P < 0.05$), Bonferroni-corrected least significant differences ($P < 0.05$) were used for post hoc mean comparisons, in which samples were compared to basal values.

Experiment 2. The purpose of experiment 2 was to assess the effect of adrenalectomy on the subsequent development of partner preferences in female prairie voles. We predicted that the removal of corticosterone, via adrenalectomy, would facilitate the formation of partner preferences and that injections of exogenous corticosterone would inhibit the formation of partner preferences.

Each female was paired with a male partner for a 1-h cohabitation period, followed immediately by a partner preference test, in which the female could elect to spend time alone, with the cohabitating partner, or with a comparable stranger. Pilot work had indicated that adrenally intact females did not develop preferences for a partner in this time period.

Adrenal glands were surgically removed ($n = 16$), or a sham operation was performed ($n = 11$). An additional group of adrenalectomized animals received an i.p. replacement injection of 500 μg of corticosterone prior to cohabitation ($n = 13$). Untreated control animals also were tested ($n = 11$).

Bilateral adrenalectomies and sham adrenalectomies were performed under sodium pentobarbital anesthesia 48 h prior to behavioral testing. After surgery, both adrenalectomized and sham-adrenalectomized animals were provided with a bottle containing 3% (wt/vol) NaCl and a separate bottle of tap water.

Completeness of the adrenalectomies was assessed by examining the adrenal glands under a dissecting microscope to determine whether the adrenal was removed with the capsule intact. Also, corticosterone blood levels were measured at the end of the preference test. Data from adrenalectomized animals were included in the analysis only if the adrenal was removed with the capsule intact and corticosterone levels were less than 50 ng/ml. [Basal levels of corticosterone are 600–1000 ng/ml for female prairie voles (Tables 1 and 2)].

Partner preferences for each experimental female were assessed through the use of a three-chambered apparatus (13). This apparatus consisted of two parallel stimulus chambers, each of which was adjoined to a third neutral chamber by a hollow tube. The experimental animal was free to move among all three chambers. The partner of the experimental animal was loosely tethered in one of the parallel chambers and the stranger was tethered in the other parallel chamber. The partner was operationally defined as the animal with which the experimental animal had been paired immediately prior to the preference test. The stranger had not previously encountered the experimental animal and was otherwise matched to the partner in terms of age, size, and reproductive status. The 3-h preference tests were monitored by using time-lapse video taping and scored by an experimentally uninformed observer, for the following parameters: (*i*) duration of physical contact between the experimental subject and the partner or stranger; (*ii*) activity, measured as the frequency of entry into the neutral cage; and (*iii*) frequency of aggression, including the incidence of threats, attacks, or fights. Social preferences in each treatment group were assessed by a paired *t* test comparing the mean time spent in physical contact with the partner vs. the stranger. Total time spent in physical contact with the stimulus animals (partner + stranger) and activity were compared among treatment groups by using ANOVA. Aggression occurred so rarely that it did not warrant statistical analysis.

Experiment 3. To assess further the behavioral effects of increased corticosterone levels on the development of partner preferences, females with intact adrenals received an i.p. injection of corticosterone (2 μg, $n = 12$; 20 μg, $n = 11$; or 200 μg, $n = 10$) or the vehicle [20% (vol/vol) propylene glycol in PBS; $n = 11$) or remained as a noninjected control ($n = 12$). These females were then allowed a 3-h cohabitation period with an unfamiliar male. Pilot work indicated that most untreated females established a preference for the familiar male after 3 h of cohabitation. Immediately after the cohab-

Table 1. Corticosterone levels in female prairie voles as a function of the social history of the female (socially naive or previously paired with a male), after exposure to an unfamiliar ("novel") male or female

Social history of animals used		Corticosterone level of experimental animals after social exposure, ng/ml				
Experimental	Stimulus	Basal level	15 min	30 min	60 min	180 min
Naive female	Unfamiliar male	828 ± 75 (7)	676 ± 73 (10)	760 ± 127 (12)	377 ± 37* (9)	339 ± 65* (10)
Naive female	Unfamiliar female	846 ± 132 (6)	945 ± 139 (11)	749 ± 100 (10)	689 ± 96 (10)	637 ± 96 (10)
Paired female	Unfamiliar male	682 ± 86 (10)	1054 ± 188 (10)	744 ± 198 (10)	1506 ± 404 (10)	1081 ± 321 (8)

Serum was sampled 15, 30, 60, or 180 min after exposure to the unfamiliar animal. Data are the mean ± SEM; group sizes are in parentheses.
*Significantly different from basal levels at $P < 0.05$.

Table 2. Corticosterone levels as a function of exposure to the stress of swimming or to injection of corticosterone (200 μg) in female prairie voles

Sample	Corticosterone, ng/ml
No treatment	823 ± 150
Swim stress	1567 ± 134
Time after corticosterone injection	
1 h	1389 ± 177
3 h	1275 ± 129

All groups contained 10 female prairie voles. In the swim stress group, females were placed in water at room temperature for 3 min, and blood samples were taken at various times after swimming. The maximal increase in corticosterone, shown here, occurred at 30 min after swimming. Corticosterone injections were administered i.p. at 1 or 3 h prior to serum collection. Untreated animals were simply removed from their cages. Serum was sampled under Metofane anesthesia and samples were taken within 1.5 min of the onset of the procedure.

itation period a preference test was conducted and social preferences were assessed as described above.

In preparation for experiment 3, a pilot study was conducted to verify that these injections were within the physiological range for female prairie voles. Serum levels of corticosterone in adrenally intact females after treatment with corticosterone were compared to serum levels obtained after exposure to a moderate stressor. Serum levels were sampled at 1 or 3 h after an i.p. injection of 200 μg of corticosterone and were compared to those obtained in comparable females given a 3-min swim test (Table 2). Maximal changes in corticosterone after the stress of swimming were measured 30 min after the onset of swimming and are shown in Table 2. Untreated females were sampled immediately upon removal from their home cages.

Experiment 4. Corticosterone treatment could influence not only the formation of social preferences but also the expression of preferences. Experiment 4 was designed to examine the possibility that corticosterone treatment might interfere with the expression of a partner preference. A female and a male were allowed to cohabitate for 6 h to allow time for the development of a reliable preference and then the female was injected with either 200 μg of corticosterone (n = 12) or the vehicle (n = 11). A noninjected control group also was tested (n = 11).

RESULTS

Experiment 1. Socially naive females responded with a significant decline in serum levels of corticosterone measured after 60 and 180 min of exposure to an unfamiliar male [$F(4,43)$ = 5.95; P = 0.0007; Table 1]. Serum corticosterone levels did not change significantly after exposure of socially naive females to unfamiliar females [$F(4,42)$ = 1.25; P = 0.31] or previously paired females to unfamiliar males [$F(4,39)$ = 1.8; P = 0.15]. Prior to male exposure, corticosterone levels did not differ significantly in singly housed vs. pair-housed females.

Experiment 2. After 1 h of cohabitation (Fig. 1), reliable preferences for the familiar partner were exhibited by adrenalectomized females (t = 9.19; P = 0.0001). No social preference for either the partner or the stranger was observed in sham-adrenalectomized females (t = 0.12; P = 0.90), adrenalectomized females receiving exogenous corticosterone replacement (t = 0.08; P = 0.93), or control females (t = 0.40; P = 0.69). Neither the total amount of time the experimental animals spent in physical contact with the stimulus animals nor activity, as measured by the mean number of entries into the neutral cage, differed among the groups [$F(3,47)$ = 0.88; P = 0.46 and $F(3,47)$ = 2.65; P = 0.06, respectively].

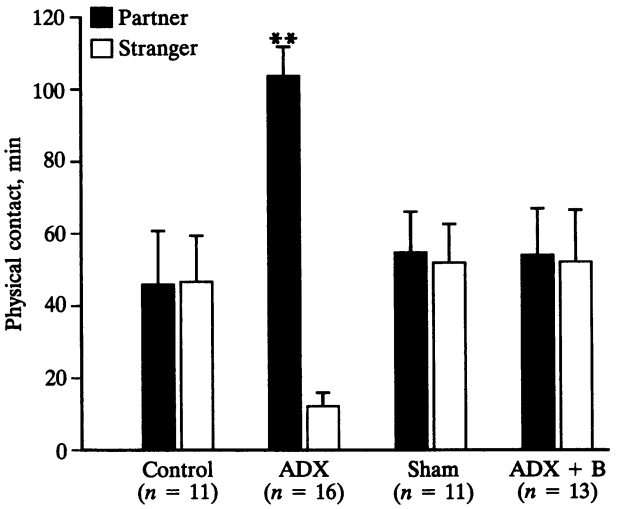

FIG. 1. After 1 h of cohabitation, adrenalectomized (ADX) females exhibited a significant preference for a familiar partner during a 3-h preference test. Females that had not received any treatment prior to the cohabitation (Control), sham-adrenalectomized females (Sham), and adrenalectomized females that received a replacement dose of 500 μg of corticosterone prior to cohabitation (ADX + B) did not display a preference for either stimulus animal. Data are the mean ± SEM. **, Significant difference at $P < 0.01$ when partner is compared to stranger.

Experiment 3. After 3 h of cohabitation (Fig. 2), a preference for the familiar partner was displayed by control females receiving either no treatment (t = 2.93; P = 0.02) or an injection of the vehicle (t = 4.23; P = 0.002). Experimental animals that received the lowest dose of corticosterone (2 μg) did not display a significant preference for either stimulus animal (t = 1.06; P = 0.34). A social preference for the unfamiliar stimulus male was observed in females that were treated with 20 μg of corticosterone (t = 2.69; P = 0.02) or 200 μg of corticosterone (t = 3.15; P = 0.01). Again, general

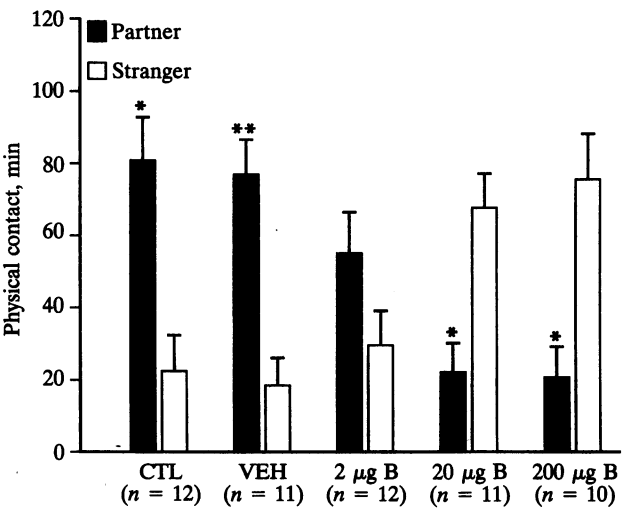

FIG. 2. After a 3-h cohabitation, noninjected controls (CTL) and vehicle-treated females (VEH) exhibited a preference for the partner during a 3-h preference test. Females that received 2 μg of corticosterone (2 μg B) prior to the cohabitation did not display a preference for either stimulus animal. Females that had received the higher doses of corticosterone (20 μg B or 200 μg B) spent significantly more time in physical contact with the unfamiliar stimulus animal. Data are the mean ± SEM. * and **, Significant differences at $P < 0.05$ and $P < 0.01$, respectively, when partner is compared to stranger.

activity and the total amount of time the experimental animals spent in physical contact with the stimulus animals did not vary significantly [$F(4,51) = 1.9$; $P = 0.12$; and $F(4,51) = 0.59$; $P = 0.67$, respectively].

Experiment 4. Injection of corticosterone at the end of a 6-h cohabitation (Fig. 3) did not interfere with the expression of a preference for the familiar partner (200 μg of corticosterone; $t = 2.83$; $P = 0.02$). Partner preferences also were expressed by females that were not treated ($t = 4.29$; $P = 0.002$) and that were treated with a vehicle ($t = 2.35$; $P = 0.04$). There were no significant differences among the three treatment groups in the amount of time spent in physical contact with the stimulus animals [$F(2,31) = 1.18$; $P = 0.32$] or in the levels of activity [$F(2,31) = 0.45$; $P = 0.64$].

DISCUSSION

The findings of experiment 1 (Table 1) confirmed an earlier study, indicating that corticosterone levels in socially naive females declined after exposure to an unfamiliar male (18). In contrast, socially naive females exposed to an unfamiliar female did not exhibit significant declines in corticosterone. In previously paired females, corticosterone levels increased after exposure to an unfamiliar male. Therefore, the directional pattern of corticosterone response was specific to the social history of the experimental animal and the sex of the stimulus animal and was not a generalized response to an unfamiliar social situation.

Monogamy requires the maintenance of pair bonds during periods of separation and usually implies that females do not form simultaneous pair bonds with more than one male (20). Differential corticosterone responses in paired vs. naive animals (Table 1) could be part of a proximate mechanism by which social bond formation is restricted to unpaired animals and through which pair bonds are maintained during periods of separation.

A more direct test of the hypothesis that hormones of the hypothalamic–pituitary–adrenal axis might influence pair bonding is provided by experiments 2 and 3. Female prairie voles require 3 h or more of nonsexual cohabitation to form stable partner preferences (Fig. 2). When endogenous corticosterone was reduced via adrenalectomy, partner preferences were formed after 1 h of cohabitation (Fig. 1). The facilitating effect of adrenalectomy on pair bonding was reversed when adrenalectomized animals received an injection of corticosterone prior to cohabitation. In experiment 3 (Fig. 2), injection of corticosterone prior to the 3-h cohabitation inhibited the formation of partner preference. In fact, the social preferences of the females that received 20 μg or 200 μg of corticosterone were directed toward the stranger in the preference test. These data suggest that in addition to blocking the normal formation of a partner preference, increased adrenal activity may enhance preferences for an unfamiliar male in females without established partners.

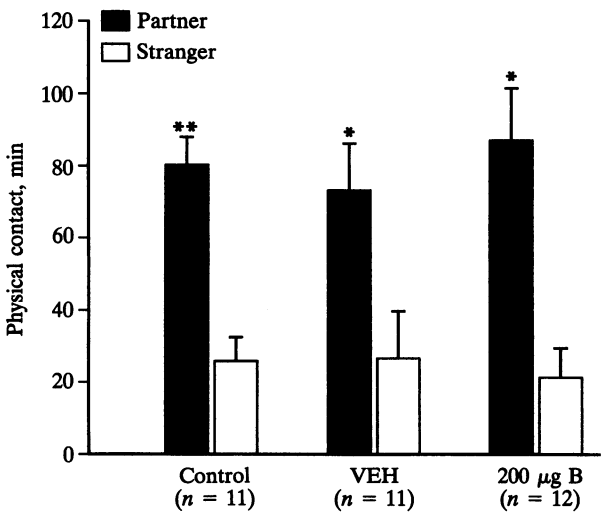

FIG. 3. To determine whether corticosterone might influence the expression, rather than the development, of partner preferences, 200 μg of corticosterone (200 μg B) was injected at the end of a 6-h cohabitation. Injections were given immediately prior to the 3-h preference test. All experimental groups exhibited partner preferences regardless of treatment and the groups did not differ. * and **, Significant differences at $P < 0.05$ and $P < 0.01$, respectively, when partner is compared to stranger.

When females with established partners were treated with corticosterone after cohabitation but immediately before the preference test (experiment 4), corticosterone no longer stimulated a social preference for the stranger. These females exhibited strong partner preferences during the preference test and did not differ significantly from the untreated females in any of the recorded parameters (Fig. 3). These results indicate that elevations in corticosterone during the preference test do not account for the group differences observed in experiment 3. Therefore, corticosterone influenced the formation of partner preferences, rather than merely inhibiting the expression of a preference for the familiar male.

In male rats, exploratory behavior (21, 22) and social interactions (23) diminish after adrenalectomy and social interactions increase after corticosterone treatment. However, exploratory behavior, as measured by movement through the neutral cage, was not affected by either adrenalectomy or corticosterone treatments in the present study, suggesting that the behavioral changes observed in prairie voles are not a consequence of changes in activity or exploratory behavior.

The behavioral findings from the present study could reflect relatively direct neural actions of the steroid hormones of the adrenal axis. These effects occurred within a few hours, possibly suggesting a nongenomic mechanism of action. In general, the behavioral effects of glucocorticoids have not been well studied. However, the discovery of neurosteroids, which are produced in the brain and interact with various neurotransmitter systems (24, 25), has drawn attention to mechanisms through which steroids may induce rapid behavioral changes. In newts, membrane receptors for glucocorticoids have been demonstrated, along with evidence that corticosterone can produce a rapid inhibition of sexual behavior in those animals (26).

Previous studies have suggested that the activation of central vasopressinergic (27) and oxytocinergic (28) pathways during sexual interactions can facilitate the development of pair bonds in male and female prairie voles (14, 15). However, it also has been shown that tactile contact releases oxytocin in rats (29). In addition, there is evidence that oxytocin and/or vasopressin may be released during stress (30, 31). Oxytocin, vasopressin, opioids, and a variety of other peptides and neurotransmitters are affected by adrenalectomy or alterations in corticosterone titers (32).

In general, research on behavioral effects of corticosteroids is limited, and to our knowledge, the effects of corticosterone on mammalian pair bonding have not been studied previously. However, research in ducklings indicates that corticosterone (33, 34) or stress (35) can inhibit the following behavior in an imprinting model. In conjunction with the present study, these findings suggest that adrenal hormones may influence the development of social attachments in both birds and mammals and that parallels may exist between the behavioral consequences of corticosterone in imprinting and in the development of adult social attachments.

In summary, in female prairie voles, partner preferences develop more rapidly when adrenal activity is inhibited either by specific social stimulation from a male or by removal of the

adrenal gland. In contrast, corticosterone replacement or supplementation inhibited the formation of preferences for a familiar male, and high levels of corticosterone treatment were associated with a preference for an unfamiliar male. These results implicate the steroid hormones of the adrenal in the modulation of partner preferences. Partner preferences, in turn, are an essential component of pair bonding, social organization, and reproduction in this monogamous mammal.

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